

What is claimed is:

1. A method for treating diabetes, insulin resistance, obesity, hyperglycemia, hyperinsulinemia, or elevated fatty acids, or glycerol, or hypertriglyceridemia which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of an aP2 inhibitor.

2. The method as defined in Claim 1 wherein the aP2 inhibitor binds to the aP2 protein and inhibits its function and/or its ability to bind free fatty acids.

3. The method as defined in Claim 1 wherein the aP2 inhibitor contains a hydrogen bond donator or acceptor group and interacts directly or through an intervening water molecule either by ionic or hydrogen bonding interactions, with one, two, or three of the three amino acid residues, designated as Arg 106, Arg 126 and Tyr 128 in human aP2 within the aP2 protein. (SEQ ID NO:1)

4. The method as defined in Claim 3 wherein the hydrogen bond donator or acceptor group is acid in nature.

5. The method as defined in Claim 3 where said aP2 inhibitor contains an additional substituent which binds to (in) and/or interacts with a discrete pocket within the aP2 protein defined roughly by the amino acid residues Phe 16, Tyr 19, Met 20, Val 23, Val 25, Ala 33, Phe 57, Thr 74, Ala 75, Asp 76, Arg 78 in human aP2.

6. The method as defined in Claim 5 wherein said additional substituent in said aP2 inhibitor is hydrophobic in nature.

7. The method as defined in Claim 5 in which the through space distance from the hydrogen bond donor/acceptor group and the additional substituent group in said aP2 inhibitor is within the distance of about 7 to about 15 Angstroms.

8. The method as defined in Claim 1 wherein Type II diabetes is treated.

9. The method as defined in Claim 1 wherein the aP2 inhibitor is employed in the form of a pharmaceutically acceptable salt thereof or a prodrug ester thereof.

10. The method as defined in Claim 1 wherein the aP2 inhibitor includes an oxazole or analogous ring, a pyrimidine derivative or a pyridazinone derivative.

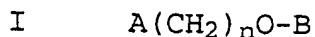
11. The method as defined in Claim 10 wherein the aP2 inhibitor is a substituted benzoyl or biphenyl-2-oxazole-alkanoic acid derivative, an oxazole derivative, a 2-thio-4,5-diphenyloxazole-S-derivative, a phenyl-heterocyclic oxazole derivative, a diaryloxazole derivative, a 4,5-diphenyloxazole derivative, an oxazole carboxylic acid derivative, a phenyloxazolyloxazole derivative, or a 2-(4,5-diaryl)-2-oxazolyl substituted phenoxyalkanoic acid derivative.

12. The method as defined in Claim 10 wherein the aP2 inhibitor is a 2-benzyloxypyrimidine derivative, a dihydro(alkylthio)(naphthylmethyl)oxypyrimidine derivative, a thiouracil derivative, or an  $\alpha$ -substituted pyrimidine-thioalkyl or alkyl ether derivative.

13. The method as defined in Claim 10 wherein the aP2 inhibitor is a pyridazinone acetic acid derivative.

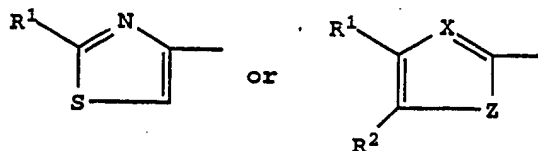
14. The method as defined in Claim 10 wherein the aP2 inhibitor is

(I) a substituted benzoylbenzene or biphenyl alkanolic acid derivative having the structure:



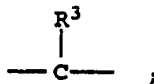
wherein

A is a group having the formula

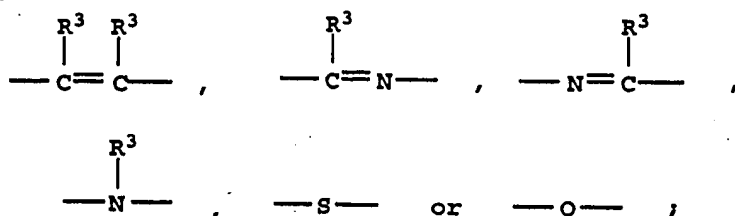


wherein

X is -N- or



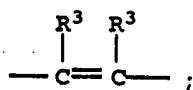
Z is



5

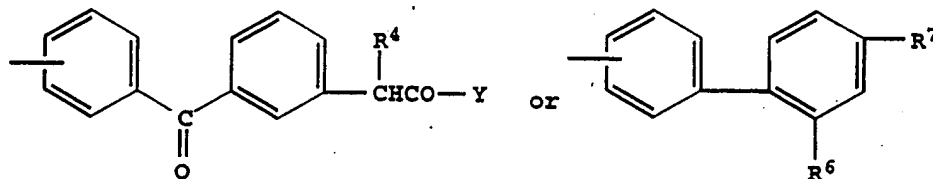
R<sup>1</sup> is hydrogen, lower alkyl or phenyl;R<sup>2</sup> is hydrogen or lower alkyl; orR<sup>1</sup> and R<sup>2</sup> taken together form a benzene ring, with the proviso that when X is -N-, Z is other than

10

R<sup>3</sup> is hydrogen or lower alkyl;

n is 1-2;

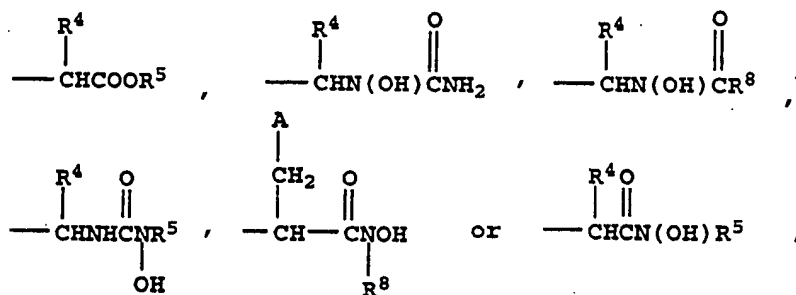
B is



15 wherein

Y is OR<sup>5</sup> or N(OH)R<sup>8</sup>;R<sup>4</sup> and R<sup>5</sup> are each, independently, hydrogen or lower alkyl;R<sup>6</sup> is hydrogen, halo or nitro;

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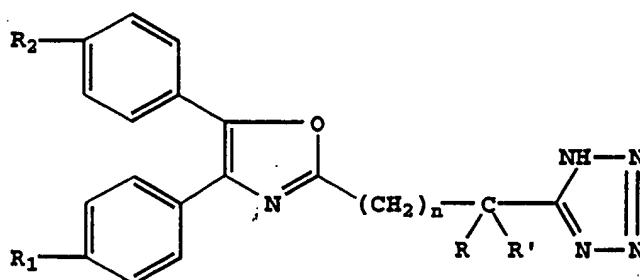
R<sup>7</sup> isR<sup>8</sup> is lower alkyl;

m is 0-3;

25 or a pharmacologically acceptable salts thereof;

(II) oxazole derivatives which have the structure

II



in which;

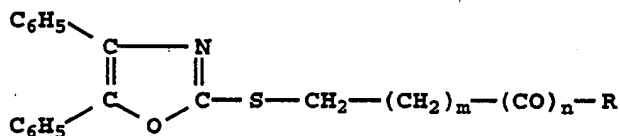
R and R' are identical or different and represent a  
5 hydrogen atom or an alkyl radical containing 1 or 2 carbon  
atoms,

R<sub>1</sub> and R<sub>2</sub> are identical or different and represent  
hydrogen or halogen atoms or alkyloxy radicals in which the  
alkyl portion contains 1 to 4 carbon atoms in a straight or  
10 branched chain, and

n equals 3 to 6, as well to their salts;

(III) 2-thiol-4,5-diphenyloxazole S-derivatives  
which have the structure

III



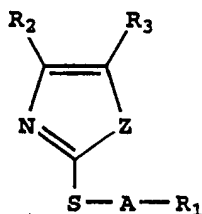
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wherein m is 0, 1 or 2, n is 1 and R represents hydroxy,  
alkoxy or amino, and pharmaceutically acceptable addition  
salts thereof;

(IV) azole derivatives of the structure

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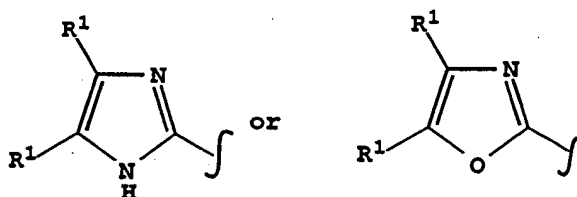
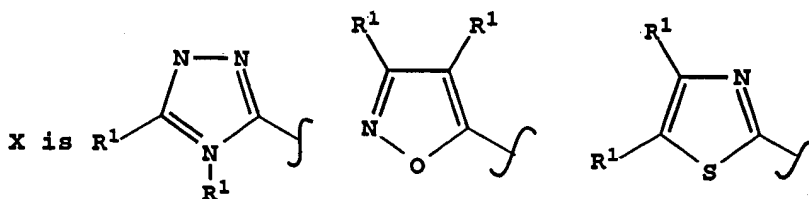
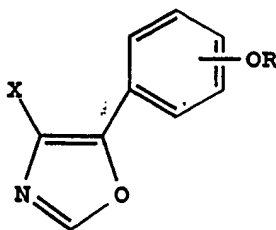
IV



wherein R<sub>1</sub> is carboxyl, esterified carboxyl or other  
functionally modified carboxyl group; R<sub>2</sub> and R<sub>3</sub> each are  
aryl of up to 10 carbon atoms; A is C<sub>n</sub>H<sub>2n</sub> in which n is an  
25 integer from 1 to 10, inclusive; and Z is O or S, and  
physiologically acceptable salts thereof;

(V) phenyl-heterocyclic oxazole derivatives which have the structure

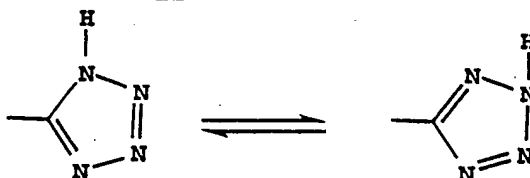
V



R is  $\text{CH}_2\text{R}^2$ ;

$\text{R}^1$  is Ph or Th;

$\text{R}^2$  is



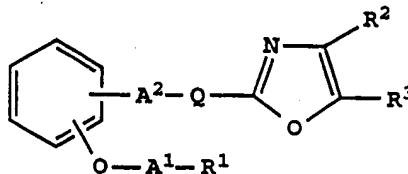
$\text{CO}_2\text{R}^3$ ; and

$\text{R}^3$  is H, or  $\text{C}_1\text{-C}_4$  lower alkyl;

or pharmaceutically acceptable salt thereof;

(VI) diaryloxazole derivatives having the structure

VI



15 wherein  $\text{R}^1$  is carboxy or protected carboxy,

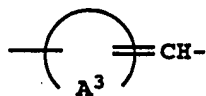
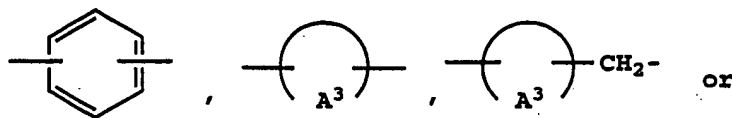
$\text{R}^2$  is aryl,

$\text{R}^3$  is aryl,

$\text{A}^1$  is lower alkylene,

A<sup>2</sup> is bond or lower alkylene and

-Q- is

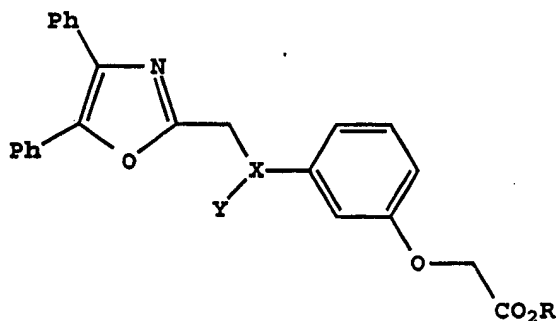


(in which is cyclo (lower)alkane or cycle(lower)alkene,

each of which may have suitable substituent(s));

(VII) 4,5-diphenyloxazole derivatives having the structure

VIIA



wherein

R is H or C<sub>1</sub>-C<sub>5</sub> lower alkyl,

X is N or CH,

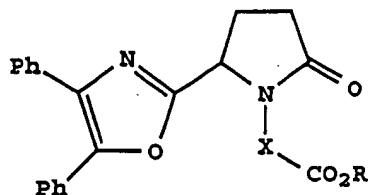
Y is H or CO<sub>2</sub>R<sup>1</sup>, or COR<sup>2</sup>, provided that when X is CH,

Y is not H,

R<sup>1</sup> is C<sub>1</sub>-C<sub>5</sub> lower alkyl, or phenylmethyl, and

R<sup>2</sup> is C<sub>1</sub>-C<sub>5</sub> alkyl;

VIIB



wherein

R is H or C<sub>1</sub>-C<sub>5</sub> lower alkyl,

X is  $(\text{CH}_2)_n$  or para or meta substituted phenyl  
wherein the substituent is  $\text{OR}^2$ ,

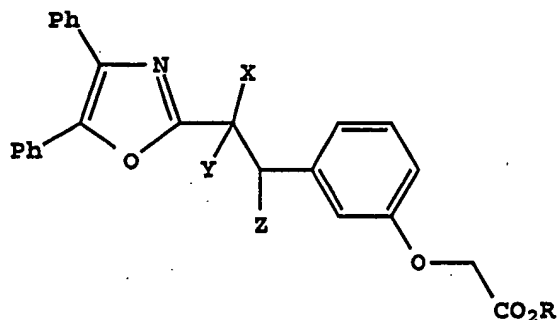
$\text{R}^2$  is  $\text{C}_1$ - $\text{C}_5$  alkyl, and

n is an integer of 4 to 8,

5 and pharmaceutically acceptable salts thereof;

(VIII) oxazole carboxylic acid derivatives having  
the structure

VIII



10

wherein

Y and Z are independently hydrogen or together form  
a bond;

X is  $\text{CN}$ ,  $\text{CO}_2\text{R}^1$  or  $\text{CONR}^2\text{R}^3$ ;

15

R and  $\text{R}^1$  are independently or together H, Na, or  
 $\text{C}_1$ - $\text{C}_5$  lower alkyl;

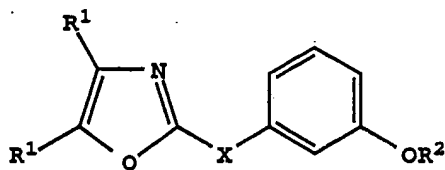
$\text{R}^2$  and  $\text{R}^3$  are independently or together H, or  $\text{C}_1$ - $\text{C}_5$   
lower alkyl;

or alkali metal salt thereof;

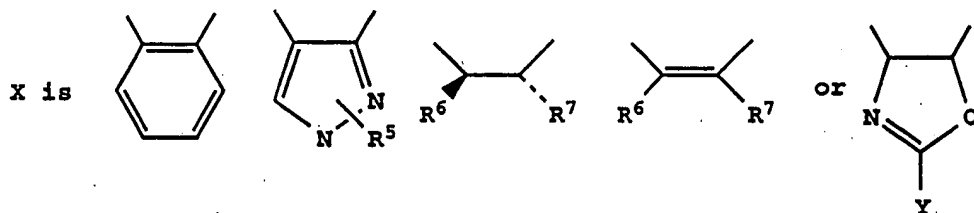
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(IX) phenyloxazolyloxazole derivatives having the  
structure

IX

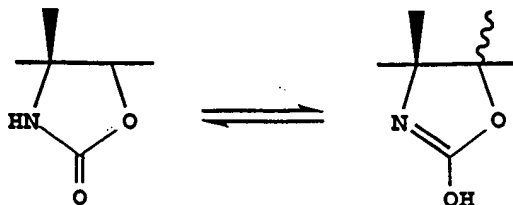


wherein



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Y is CH<sub>3</sub>, Ph, or OH, provided that when Y is OH, the compound exists in the keto-enol tautomerism form

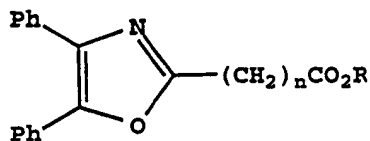


- 5      R<sup>1</sup> is Ph or Th;  
       R<sup>2</sup> is CH<sub>2</sub>R<sup>3</sup>;  
       R<sup>3</sup> is CO<sub>2</sub>R<sup>4</sup>;  
       R<sup>4</sup> is H or C<sub>1</sub>-C<sub>5</sub> lower alkyl;  
       R<sup>5</sup> is H or CH<sub>3</sub>; R<sup>6</sup> is OHCHN or H<sub>2</sub>N; and  
       R<sup>7</sup> is H or OH;

10 or pharmaceutically acceptable salt thereof;

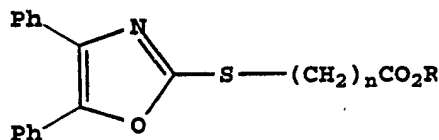
(X) 2-(4,5-diaryl)-2-oxazolyl substituted phenoxyalkanoic acids and esters having the structure

XA



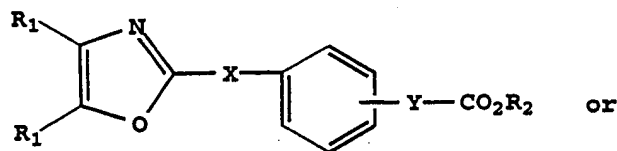
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XB



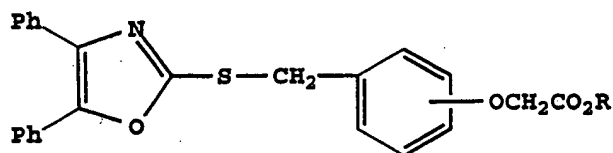
(wherein n is 7-9 and R is hydrogen or lower alkyl; or when R is hydrogen, the alkali metal salt thereof),

XC



20

XD



wherein

R<sub>1</sub> is phenyl or thienyl;



$R_2$  is hydrogen, lower alkyl or together with  $CO_2$  is tetrazol-1-yl;

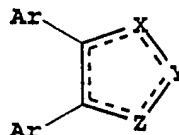
X is a divalent connecting group selected from the group consisting of  $CH_2CH_2$ ,  $CH=CH$ , and  $CH_2O$ ;

5 Y is a divalent connecting group attached to the 3- or 4-phenyl position selected from the group consisting of  $OCH_2$ ,  $CH_2CH_2$  and  $CH=CH$ ,

or when  $R_2$  is hydrogen, an alkali metal salt thereof;

(XI) substituted 4,5-diaryl heterocycles having the  
10 formula

XI



in which

each group Ar is the same or different and is  
15 optionally substituted phenyl or optionally substituted heteroaryl;

X is nitrogen or  $CR^1$ ;

Y is nitrogen,  $N(CH_2)_nA$  or  $C(CH_2)_nA$ ;

Z is nitrogen, oxygen or  $N(CH_2)_nA$ , and the dotted  
20 line indicates the optional presence of a double bond so as to form a fully unsaturated heterocyclic ring;

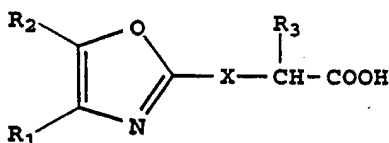
$R^1$  is hydrogen,  $C_{1-4}$ alkyl, optionally substituted phenyl or optionally substituted heteroaryl;

n is 4 to 12; and

25 A is  $CO_2H$  or a group hydrolysable to  $CO_2H$ , 5-tetrazolyl,  $SO_3H$ ,  $P(O)(OR)_2$ ,  $P(O)(OH)_2$ , or  $P(O)(R)(OR)$  in which R is hydrogen or  $C_{1-4}$ alkyl, or a pharmaceutically acceptable salt thereof;

(XII) compounds which have the structure

30 XII



Where X is O or S;

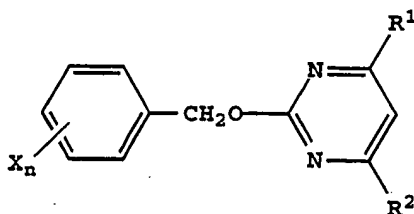
$R_1$  is H, phenyl or phenyl substituted with F, Cl or Br or alkoxy,

$R_2$  is H, alkyl, phenyl or phenyl substituted with F, Cl or Br or alkoxy, and

5  $R_3$  is H or alkyl;

(XIII) 2-benzyloxypyrimidine derivatives having the following structure

XIII



10 wherein

$R^1$  and  $R^2$  are each independently H, a halogen, hydroxyl,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl,  $C_3$ - $C_5$  alkenyl,  $C_3$ - $C_5$  alkynyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  haloalkoxy,  $C_3$ - $C_5$  alkenyloxy,  $C_3$ - $C_5$  alkynyloxy,  $C_1$ - $C_4$  alkylthio, or phenyl, with the

15 proviso that at least one of  $R^1$  and  $R^2$  must be hydroxyl;

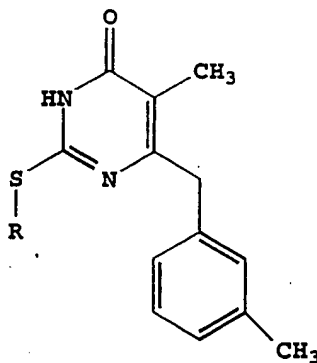
$n$  is an integer of 0 to 5; and

each X which may be identical or different if  $n$  is greater than 1, is a halogen,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  haloalkyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkylthio,  $C_7$ - $C_9$  aralkyloxy, phenyl,

20 hydroxymethyl, hydroxycarbonyl,  $C_1$ - $C_4$  alkoxy carbonyl, or nitro;

(XIV) dihydro(alkylthio)-(naphthylmethyl)-oxypyrimidines which have the structures

XIVA



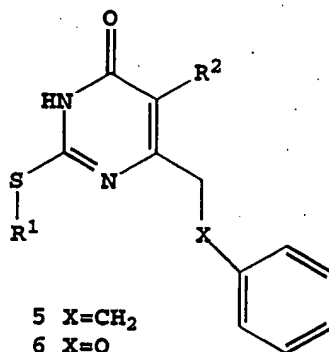
3a R=sec-butyl

3b R=cyclopentyl

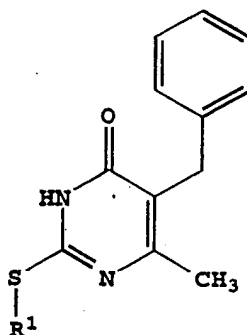
3c R=cyclohexyl

LA24a

XIVB

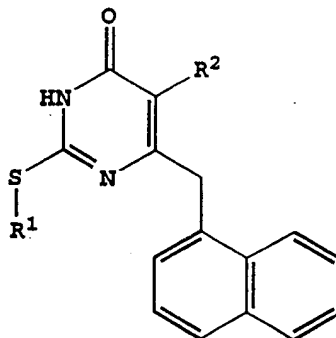


XIVC

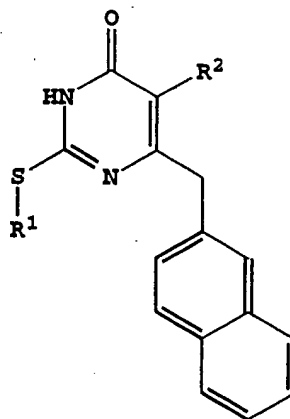


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XIVD



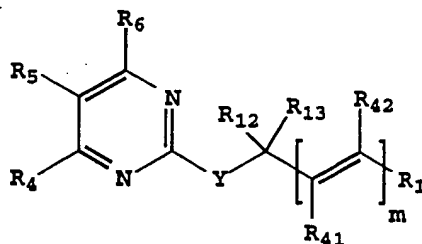
XIVE



- R<sup>1</sup> = sec-butyl, cyclopentyl, cyclohexyl;  
10 R<sup>2</sup> = H, CH<sub>3</sub>, including tautomers of the above;

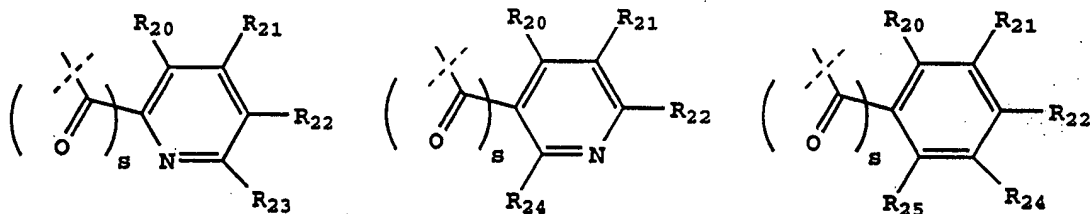
(XVI)  $\alpha$ -substituted pyrimidine-thioalkyl and alkylether compounds which have the structure

XVI



5 where  $m$  is 0 or 1;

$R^1$  is selected from  $-\text{CO}_2\text{R}_{53}$ ,  $-\text{CONR}_{54}\text{R}_{55}$ ,



- where  $s$  is 0 or 1, and  $R_{20}$ ,  $R_{21}$ ,  $R_{22}$ ,  $R_{23}$ ,  $R_{24}$ , and  $R_{25}$  are the same or different and are selected from  $-\text{H}$ ,  $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_1\text{-C}_6$  alkenyl,  $\text{C}_1\text{-C}_6$  alkoxy,  $\text{C}_1\text{-C}_6$  alkylthio,  $\text{C}_3\text{-C}_8$  cycloalkyl,  $-\text{CF}_3$ ,  $-\text{NO}_2$ ,  $-\text{halo}$ ,  $-\text{OH}$ ,  $-\text{CN}$ , phenyl, phenylthio,  $-\text{styryl}$ ,  $-\text{CO}_2(\text{R}_{31})$ ,  $-\text{CON}(\text{R}_{31})(\text{R}_{32})$ ,  $-\text{CO}(\text{R}_{31})$ ,  $-(\text{CH}_2)_n\text{-N}(\text{R}_{31})(\text{R}_{32})$ ,  $-\text{C}(\text{OH})(\text{R}_{31})(\text{R}_{33})$ ,  $-(\text{CH}_2)_n\text{N}(\text{R}_{31})(\text{CO}(\text{R}_{33}))$ ,  $(\text{CH}_2)_n\text{N}(\text{R}_{31})(\text{SO}_2(\text{R}_{33}))$ , or where  $R_{20}$  and  $R_{21}$ , or  $R_{21}$  and  $R_{22}$ , or  $R_{22}$  and  $R_{23}$  are taken together to form a five or six-membered saturated or unsaturated ring containing 0 or 1 oxygen, nitrogen or sulfur, where the unsaturated ring may be optionally substituted with 1, 2 or 3,  $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_1\text{-C}_6$  alkoxy,  $-\text{OH}$ ,  $-\text{CH}_2\text{OH}$ ,  $-(\text{CH}_2)_n\text{-N}(\text{R}_{31})(\text{R}_{32})$ ,  $-\text{C}_3\text{-C}_8$  cycloalkyl,  $-\text{CF}_3$ ,  $-\text{halo}$ ,  $\text{CO}_2(\text{R}_{31})$ ,  $-\text{CON}(\text{R}_{31})(\text{R}_{32})$ ,  $-\text{CO}(\text{R}_{31})$ ,  $-(\text{CH}_2)_n\text{N}(\text{R}_{31})(\text{CO}(\text{R}_{33}))$ ,  $-(\text{CH}_2)_n\text{N}(\text{R}_{31})(\text{SO}_2(\text{R}_{33}))$ ,  $-\text{CN}$ ,  $-\text{CH}_2\text{CF}_3$  or  $-\text{CH}(\text{CF}_3)_2$ , or phenyl and the saturated ring may be optionally substituted with 1, 2 or 3,  $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_1\text{-C}_6$  alkoxy,  $-\text{OH}$ ,  $-\text{CH}_2\text{OH}$  or  $-(\text{CH}_2)_n\text{-N}(\text{R}_{31})(\text{R}_{32})$  or one oxo ( $=\text{O}$ );

where  $n$  is 0-3 and  $R_{31}$ ,  $R_{32}$  and  $R_{33}$  are the same or different and are selected from

$-\text{H}$ ,

$\text{C}_1\text{-C}_6$  alkyl,

phenyl optionally substituted with 1, 2 or 3 -halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -CF<sub>3</sub>, -OH or -CN,

or where R<sub>31</sub> and R<sub>32</sub> taken together with the attached nitrogen to form a ring selected from -pyrrolidinyl, -  
 5 piperidinyl, -4-morpholinyl, -4-thiomorpholinyl, -4-piperazinyl, -4-(1-C<sub>1</sub>-C<sub>6</sub>alkyl)piperazinyl, or a member selected from

1-cyclohexenyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-imidazolyl, 4-imidazolyl, 2-benzothiazolyl,  
 10 2-benzoxazolyl, 2-benzimidazolyl, 2-oxazolyl, 4-oxazolyl, 2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 5-methyl-3-isoxazolyl, 5-phenyl-3-isoxazolyl, 4-thiazolyl, 3-methyl-2-pyrazinyl, 5-methyl-2-pyrazinyl, 6-methyl-2-pyrazinyl, 5-chloro-2-thienyl, 3-furyl, benzofuran-2-yl, benzothien-2-  
 15 yl, 2H-1-benzopyran-3-yl, 2,3-dihydrobenzopyran-5-yl, 1-methylimidazol-2-yl, quinoxalin-2-yl, piperon-5-yl, 4,7-dichlorobenzoxazol-2-yl, 4,6-dimethylpyrimidin-2-yl, 4-methylpyrimidin-2-yl, 2,4-dimethylpyrimidin-6-yl, 2-methylpyrimidin-4-yl, 4-methylpyrimidin-6-yl, 6-  
 20 chloropiperon-5-yl, 5-chloroimidazol[1,2-a]pyridin-2-yl, 1-H-inden-3-yl, 1-H-2-methyl-inden-2-yl, 3,4-dihydronaphth-1-yl, S-4-isopropenylcyclohexen-1-yl or 4-dihydronaphth-2-yl;

where R<sub>53</sub> is selected from -H, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, phenyl (optionally substituted with 1, 2, or  
 25 3 -halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -CF<sub>3</sub>, -OH, -CN), or a five or six-membered unsaturated ring containing 0 or 1 oxygen, nitrogen or sulfur, where the unsaturated ring may be optionally substituted with -H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -OH, -CH<sub>2</sub>OH, or -(CH<sub>2</sub>)<sub>n</sub>-N(R<sub>31</sub>)(R<sub>32</sub>);

30 where R<sub>54</sub> and R<sub>55</sub> being the same or different are selected from -H, C<sub>1</sub>-C<sub>6</sub> alkyl, allyl, or phenyl (optionally substituted with 1, 2 or 3 -halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy or -CF<sub>3</sub>), or taken together with the attached nitrogen to form a ring selected from -pyrrolidinyl, -piperidinyl, -4-morpholinyl, -4-thiomorpholinyl, -4-piperazinyl, -4-(1-C<sub>1</sub>-  
 35 C<sub>6</sub>alkyl)piperazinyl;

R<sub>41</sub> and R<sub>42</sub>, being the same or different, are selected from -H and C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>12</sub> is selected from -H, C<sub>1</sub>-C<sub>6</sub> alkyl, -C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -CN, -C(O)NH<sub>2</sub>, -C(O)N(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl), -  
5 CO<sub>2</sub>H, -CO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -CH<sub>2</sub>OH, -CH<sub>2</sub>NH<sub>2</sub> or -CF<sub>3</sub>;

R<sub>13</sub> is selected from -H, C<sub>1</sub>-C<sub>6</sub> alkyl or -CF<sub>3</sub>;

Y is selected from -S-, -S(O)-, -S(O)<sub>2</sub>, or -O-;

R<sub>4</sub> is -OH;

R<sub>5</sub> is selected -H, -C<sub>2</sub>H<sub>4</sub>OH, -C<sub>2</sub>H<sub>4</sub>-O-TBDMS, halo, -C<sub>3</sub>-  
10 C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, -CH<sub>2</sub>CH<sub>2</sub>Cl or C<sub>1</sub>-C<sub>4</sub> alkyl, with the proviso that R<sub>5</sub> is not isobutyl;

or, when R<sub>6</sub> is hydroxyl, R<sub>4</sub> and R<sub>5</sub> are taken together to form a five or six-membered saturated or unsaturated ring which together with the pyrimidine ring form the group  
15 consisting of 7H-pyrrolo[2,3-d]pyrimidine, 5,6-dihydro-7H-pyrrolo[2,3-d]pyrimidine, furo[2,3-d]pyrimidine, 5,6-dihydro-furo[2,3-d]pyrimidine, thieno[2,3-d]pyrimidine, 5,6-dihydro-thieno[2,3-d]pyrimidine, 1H-pyrazolo[3,4-d]pyrimidine, 1H-purine, pyrimido[4,5-d]pyrimidine,  
20 pteridine, pyrido[2,3-d]pyrimidine, or quinazoline, where the unsaturated ring may be optionally substituted with 1, 2 or 3, C<sub>1</sub>-C<sub>6</sub> alkyl C<sub>1</sub>-C<sub>6</sub> alkoxy, -OH, -CH<sub>2</sub>OH, or -(CH<sub>2</sub>)<sub>n</sub>-N(R<sub>31</sub>)(R<sub>32</sub>), -C<sub>3</sub>-C<sub>8</sub> cycloalkyl, -CF<sub>3</sub>, -halo, -CO<sub>2</sub>(R<sub>31</sub>), -CON(R<sub>31</sub>)(R<sub>32</sub>), -CO(R<sub>31</sub>), -(CH<sub>2</sub>)<sub>n</sub>N(R<sub>31</sub>)(CO(R<sub>33</sub>)), -  
25 (CH<sub>2</sub>)<sub>n</sub>N(R<sub>31</sub>)(SO<sub>2</sub>(R<sub>33</sub>)), and the saturated ring may be optionally substituted with 1, 2 or 3, -C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -OH, -CH<sub>2</sub>OH, or -(CH<sub>2</sub>)<sub>n</sub>-N(R<sub>31</sub>)(R<sub>32</sub>) or one oxo (=O); and

R<sub>6</sub> is selected from -H, -OH, halo, -CN, -CF<sub>3</sub>, -  
30 CO<sub>2</sub>(R<sub>61</sub>), -C(O)R<sub>61</sub> or -C(O)N(R<sub>61</sub>)(R<sub>62</sub>) where R<sub>61</sub> and R<sub>62</sub> are the same or different and are selected from

-H,

C<sub>1</sub>-C<sub>6</sub> alkyl,

phenyl optionally substituted with 1, 2 or 3 -halo,

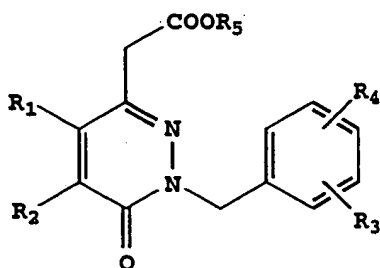
35 C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -CF<sub>3</sub>, -OH, -CN,

or where R<sub>61</sub> and R<sub>62</sub> taken together with the attached nitrogen to form a ring selected from -pyrrolidinyl, -

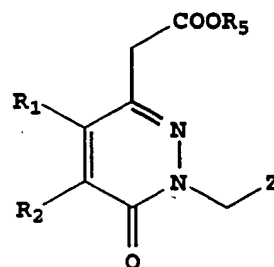
piperidinyl, -4-morpholinyl, -4-thiomorpholinyl, -4-piperazinyl, or -4-(C<sub>1</sub>-C<sub>6</sub> alkyl)piperazinyl;

pharmaceutically acceptable salts, hydrates, N-oxides and solvates thereof;

5 (XVII) compounds which have the structure



XVIIA



XVIIIB

where R<sub>1</sub> and R<sub>2</sub> are H, alkyl, aryl or arylalkyl, where the alkyl can include as substituents halogen, CF<sub>3</sub>, CH<sub>3</sub>O, CH<sub>3</sub>S, NO<sub>2</sub>, or R<sub>1</sub> and R<sub>2</sub> with the carbons to which they are attached can form methylenedioxy, or

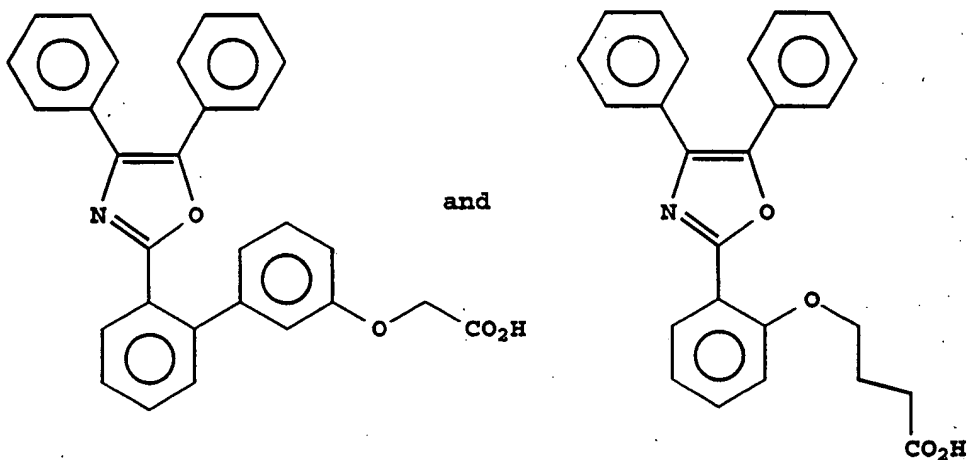
R<sub>1</sub> and R<sub>2</sub> can form a C<sub>3</sub>-C<sub>7</sub> non-aromatic ring, or a heterocycle which can be pyridine, pyrazine, pyrimidine, pyridazine, indol, or pyrazole, or an oxygen containing heterocycle which can be pyran or furan, or a sulfur containing heterocycle which can be thiopyran, or thiophene; the heterocycles being optionally substituted with halogen or alkyl,

R<sub>3</sub> and R<sub>4</sub> are H, alkyl, halogen, CF<sub>3</sub>, CH<sub>3</sub>O, CH<sub>3</sub>S or NO<sub>2</sub> or R<sub>3</sub> and R<sub>4</sub> with the carbons to which they are attached can form a methylenedioxy group,

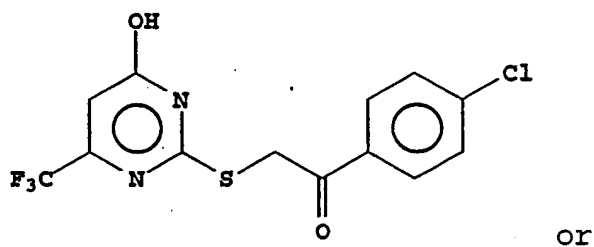
R<sub>5</sub> is H, and

Z is a heterocycle which can be pyridine, thiazole, benzothiazole, benzimidazole or quinoline, which Z group can optionally be substituted with halogen or alkyl.

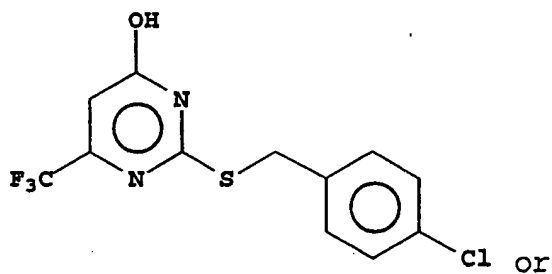
15. The method as defined in Claim 1 wherein the aP2 inhibitor has the structure



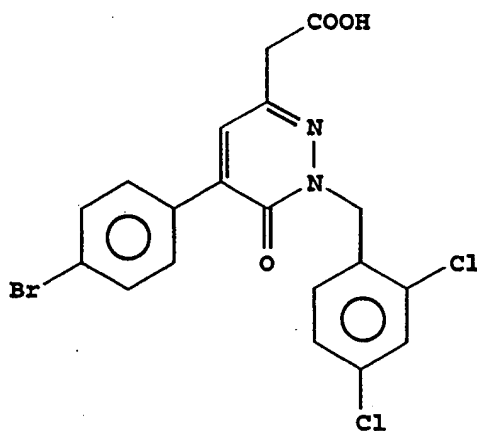
5



or



or



10



16. A pharmaceutical combination comprising an  $\alpha$ P2 inhibitor and another type antidiabetic agent.

17. The combination as defined in Claim 16 wherein  
5 the antidiabetic agent is a biguanide, a sulfonyl urea, a glucosidase inhibitor, a thiazolidinedione, an insulin sensitizer, a glucagon-like peptide-1 (GLP-1), insulin, a PPAR  $\alpha/\gamma$  dual agonist and/or a meglitinide.

18. The combination as defined in Claim 16 wherein  
10 the antidiabetic agent is metformin, glyburide, glimepiride, glipyrider, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, troglitazone, insulin, KRP-297, repaglinide and/or nataglinide.

19. The combination as defined in Claim 16 wherein  
15 the  $\alpha$ P2 inhibitor is present in a weight ratio to the antidiabetic agent within the range from about 0.01 to about 100:1.

20. A method for treating insulin resistance, diabetes, obesity, hyperglycemia, hyperinsulinemia, or  
20 elevated blood levels of free fatty acids, or glycerol, or hypertriglyceridemia, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a pharmaceutical combination as defined in Claim 16.

25